SUMMARY OF SAFETY AND PROBABLE BENEFIT
(Version 3.1 4/6/2005)

I. GENERAL INFORMATION

Device Generic Name: Intravascular occluding catheter, temporary

Device Trade Name: CoAxia NeuroFlo™ Catheter

Applicant's Name and Address: CoAxia, Inc.
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Humanitarian Device Exemption (HDE) Number: H030005

Date of Humanitarian Use Device Designation: August 15, 2002

Date(s) of Panel Recommendations: None

Date of Good Manufacturing Practice Inspection: December 16-18, 2003

Date of Notice of Approval to Applicant: March 30, 2005

II. INDICATIONS FOR USE

The CoAxia NeuroFlo™ Catheter is intended for the treatment of cerebral ischemia resulting from symptomatic vasospasm following aneurismal subarachnoid hemorrhage (SAH), secured by either surgical or endovascular intervention for patients who have failed maximal medical management.

III. CONTRAINDICATIONS

The NeuroFlo Catheter is contraindicated for use in:

- Patients with significant left ventricular dysfunction
- Patients with aortic aneurysm including those which have been treated with endovascular grafts
- Patients with a history of bleeding disorders
- Pregnant women

IV. WARNINGS AND PRECAUTIONS

The *Warnings* and *Precautions* for the NeuroFlo Catheter may be found in the NeuroFlo Catheter Instructions for Use manual.

V. DEVICE DESCRIPTION

The NeuroFlo™ Catheter is a multi-lumen device with two balloons mounted near the distal tip. The catheter is inserted over a guide wire through a vascular introducer sheath placed in the femoral artery. The device has a working length of approximately 62 cm and is coated with a hydrophilic coating. A multi-port manifold at the proximal end of the device allows balloon inflation, guide wire insertion and attachment of a pressure monitoring line. Each balloon can be inflated independently to a variable diameter to control blood flow in the descending aorta. The device has three marker bands to aid in balloon placement. The catheter is ethylene oxide (EtO) sterilized and is intended for single use only.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The treatment of patients with cerebral vasospasm following SAH includes drug treatments, generally categorized to Triple-H (hypertension, hypervolemia, hemodilution) therapy, and intra-arterial vasodilators.

Angioplasty of the spastic vessels is another option that is typically reserved for patients who are refractory to medical management. The spastic vessels are dilated mechanically using a balloon catheter.

VII. MARKETING HISTORY

The NeuroFlo Catheter received its CE mark in November 2003. The device is registered, and in current use, in Argentina.

The NeuroFlo Catheter has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Observed Adverse Effects:
In an uncontrolled clinical trial, nineteen patients with cerebral vasospasm following aneurismal subarachnoid hemorrhage (symptomatic=16, asymptomatic=2, compassionate use = 1) were treated with the NeuroFlo device. The compassionate use patient was in a

barbiturate coma and was treated based on imaging evidence of vasospasm. Adverse events are summarized in the table below for all 19 patients.

Summary Table of Adverse Events in 19 Patients

Adverse Event	N (%)
Death	6 (32)
Neurological deterioration	4 (21)
Hydrocephalus	2 (10)
Anemia	1 (5)
Sepsis	1 (5)
Psychomotor excitation	1 (5)
Groin hematoma	1 (5)
Cervical spontaneous edema	1 (5)
Urinary tract infection	1 (5)
Dyspnea	1 (5)
Transient arrhythmia	1 (5)
Coagulopathy	1 (5)
Acute Respiratory Distress Syndrome	1 (5)
Renal failure	1 (5)
Cardiogenic shock	1 (5)
Pulled out sheath	1 (5)

N = number of patients experiencing event

Potential Adverse Effects:
Although not reported during the clinical trial, other potential adverse effects associated with the NeuroFlo procedure may include:

- aortic dissection
- aortic rupture
- cardiac arrhythmias
- cardiac failure
- femoral bleeding
- hemodynamic deterioration
- intracranial hemorrhage
- renal failure
- thromboembolism
- tissue ischemia

IX. SUMMARY OF PRECLINICAL STUDIES

Preclinical testing of the NeuroFlo catheter consisted of biocompatibility testing, in-vitro (bench) testing and animal testing.

Biocompatibility Testing

Biocompatibility testing of the NeuroFlo catheter was conducted in accordance with ISO 10993 and the FDA Blue Book Memorandum G95-1 "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing". All testing was conducted in accordance with good laboratory practice (GLP) regulations (21CFR 58).

Testing was selected using the matrix provided for External Communicating Device, Circulating Blood, Limited Duration. According to the matrix, the following tests were performed:

- cytotoxicity
- sensitization
- irritation or intracutaneous reactivity
- systemic toxicity (acute)
- hemocompatibility

All testing yielded a non-toxic response.

In-Vitro (Bench) Testing

Functional (bench) testing of the NeuroFlo catheter was performed using devices, or partial assemblies, that had been subjected to all manufacturing processes, including coating and sterilization. Functional test selection was based upon ISO and EN standards and on FDA's Guidance for the Use of Short-term and Long-term Intravascular Catheters. The following tests were conducted for the NeuroFlo catheter:

1. Balloon Sizing and Burst

   Purpose: To determine the diameter of the NeuroFlo balloon at a given volume of inflation medium and to determine the volume at burst.

   Acceptance Criteria: The NeuroFlo balloon(s) must be within ± 10% of the diameter specified for a given volume of fluid.

   Test Builds: A total of 15 complete NeuroFlo catheters were used (for a total of 30 balloons).

   Protocol: Balloon sizing was performed for all balloons from 4 – 13 cc. Balloon diameter measurements were recorded at every volume up to 13 cc. After the balloon sizing is performed, additional fluid was added at 1 cc every 2 minutes until 24 cc had been added, or until the balloon failed.

   Results: The diameter of each of the 30 balloons, at each of the required inflation volumes, met the specification. Twenty-nine balloons were inflated to 24 cc for 2 minutes. One balloon failed at 24 cc prior to the 2 minute time-limit.

2. Multiple Inflation Testing

   Purpose: To verify that the NeuroFlo catheter will withstand repeated balloon inflation without failure.

   Acceptance Criteria: Each catheter must inflate 5 times without failure.

Test Builds: A total of 15 complete NeuroFlo catheters were used (for a total of 30 balloons).

Protocol: Each balloon was inflated repeatedly until failure or 5 inflation cycles, whichever occurred first.

Results: All fifteen catheters (i.e., 30 balloons), met the acceptance criteria

3. Tensile Testing

Purpose To verify that the NeuroFlo catheter bonds and materials, meet the intended design tensile specification.

Acceptance Criteria: The device must withstand ≥ 3.37 lbs. of tensile force before failure.

Test Builds: A total of 15 complete NeuroFlo catheters were used for the test.

Protocol: Each catheter was pulled at a rate of 3 in./min. The test was completed when failure of the device occurred. The mode of and location of the failure was recorded for each catheter.

Results: All fifteen catheters met the required tensile specification of 3.37 lbs. before failure.

4. Sheath Compatibility

Purpose: To verify that the NeuroFlo catheter can be used in a 9F sheath.

Acceptance Criteria: The catheter must be able to advance and withdraw through a 9F (internal diameter ≥ 0.121 in.) introducer sheath with ≤ 3.37 lbs. of force.

Test Builds: Seven complete NeuroFlo catheters were used for the test.

Protocol: The catheter was inserted through a 9F sheath until both balloons exited the distal end of the sheath; the proximal end of the catheter was attached to a Chattilon tensile fixture. The force to push the catheter through the sheath was recorded. The direction of the tensile fixture was reversed and the force to withdraw the catheter from the sheath was recorded.

Results: All seven catheters were inserted and withdrawn through the sheath within the specification.

5. Track Testing

Purpose: To verify the ability of the NeuroFlo catheter to track through a tortuous path, similar to what would be found in-vivo.

Acceptance Criteria: The catheter must advance and withdraw through the test fixture with ≤ 3.37 lbs. of force.

Test Builds: A total of 30 complete NeuroFlo catheters were used for the test.

Protocol: Each catheter was placed into the testing fixture and attached to a Chattilon force gauge at its proximal end. Each catheter was pushed through the fixture, and the peak force recorded. Once the catheter had reached the end of the fixture the direction was reversed. The peak force required to withdraw the catheter was recorded.

Results: All thirty catheters met the specification.

6. Pressure Monitoring

Purpose: To verify the ability of the NeuroFlo catheter for measuring pressure.

Acceptance Criteria: Pressure may be read through the guide wire lumen of the NeuroFlo catheter.

Test Builds: Five complete NeuroFlo catheters were used.

Protocol: The catheter was advanced through a 9F sheath until both balloons were positioned within the pressure-measuring chamber of a pressurized flow loop. The pressure within the flow loop was measured through the guide wire lumen of the NeuroFlo catheter using standard monitoring equipment and compared to the pre-set system pressure.

Results: All five catheters were able to facilitate pressure measurement through the guide wire lumen and met the specification.

7. Deflation Testing

Purpose: To determine the time required to deflate both balloons in the catheter.

Acceptance Criteria: Each balloon must fully deflate in less than 300 seconds.

Test Builds: Fifteen complete NeuroFlo catheters were used (for a total of 30 balloons).

Protocol: Each balloon was inflated with 12 cc of fluid for 2 minutes and deflated. The deflation was timed starting when vacuum was first drawn on the balloon.

Results: All thirty balloons met the required specification.

8. Coating Integrity

Purpose: This study was performed in order to determine:

- How much heparin is coated onto each device
- The activity level of the heparin on the device
- The effects, if any, that exposure to ethylene oxide sterilization may have on the coating
- What impact exposure to physiologic blood flow conditions will have on the coating.

Acceptance Criteria: None. Testing was performed for informational purposes and to benchmark current process performance.

Test Builds: There were five groups with 3 devices per group (15 devices), plus one control, for a total of 16 NeuroFlo devices tested.

Protocol: Three (3) catheters in Group 1 were coated but not sterilized. Twelve (12) catheters in Groups 2 to 5 were coated and sterilized before placement in a flow loop from 0 – 24 hours. Three catheters were removed from the loop for testing at the following time points: 0, 2, 12 and 24 hours. After removal from the loop, three sections were taken of each balloon (2 balloons per device) for assaying, for a total of 6 sample sections per device tested. The catheters not exposed to the flow loop (i.e., 0 hours and Group 1), were used for comparative purposes.

Results: There was no major difference in activity among the various test groups; i.e., non-sterile samples, sterile sample or samples exposed to

the flow loop. This provides evidence that the heparin bound to the balloons on the NeuroFlo device is functional and is not affected by EtO sterilization or by the flow loop up to 24 hours.

9. Sterility
The NeuroFlo Catheter is sterilized using 100% Ethylene Oxide (EtO). The catheter was validated to a sterility assurance level (SAL) of 10^{-6} in accordance with ANSI/AAMI/ISO 11135-1994. The validation allows the NeuroFlo Catheter to be sterilized up to 2 times.

10. Shelf Life
The NeuroFlo Catheter and its packaging were subjected to accelerated aging and have been validated for a shelf life of one year.

Animal Testing

Three animal studies were conducted.

Rodent feasibility study: The first study is a rat study using a standard rat stroke model and treatment with aortic ligation for one hour. Ligation was carried out anytime between 3 and 18 hours after stroke onset. Several methods of investigating perfusion were employed. The rats were first studied using laser doppler flow measurement of cerebral blood flow (CBF) in normal brain, the ischemic penumbra and in the core of the stroke. The results showed an increase in mean arterial pressure (MAP), but a larger increase in CBF in all regions studied. The second analysis used fluorescent dye to label capillaries after treatment and prior to decapitation. These results also showed increased capillaries in the penumbra region of the stroke compared to untreated animals. No numerical analysis was presented (number of rats, percentage increase in number of vessels, etc.) The final analysis used technetium staining to look at stroke volume. This study revealed an average reduction of stroke volume by 66% in treated animals compared to sham controls. This comparison reached statistical significance. There was no evidence of cerebral hemorrhage in any rats.

Swine feasibility study: 6 pigs were studied using the NeuroFlo Catheter at variable amounts of inflation, from 50%-100% luminal reduction (LR) of the descending aorta. It was found that CBF was increased 38% above baseline at 50% LR and 138% at 90% LR. Significant increases in MAP did not occur until 80% LR. No intra-cranial hemorrhage (ICH) was seen in the 6 pigs. In this experiment, the pigs were healthy; there was no stroke model employed.

GLP animal study: A final animal study involving 8 pigs with aortic diameters similar to humans was performed. The animals were implanted with the NeuroFlo catheter and the balloon inflated to 70% occlusion. This was continued for 2-12 hours. Flow in the middle cerebral artery (MCA) was monitored via transorbital doppler. MAP and other parameters were also monitored. After removal of the device the femoral artery used for access was ligated. The animals were euthanized after 7 days and pathological analysis conducted. The study demonstrated increased blood flow in the MCA without

significant increase in MAP. This effect slowly diminished over time with long occlusions. Two animals had arrhythmias, one had two such events. The first arrhythmia required defibrillation and the second CPR and IV epinephrine. The other animal experienced an arrhythmia and decreased blood pressure but recovered without treatment. Additionally, 4 animals did not stand on their hind legs to the expected extent after the procedure. This could have been the effect of positioning or the femoral artery ligation. Pathology did not reveal any significant evidence of end organ damage due to the procedure or the device.

X. SUMMARY OF CLINICAL INFORMATION

The study of the NeuroFlo catheter for treatment of cerebral vasospasm following aneurismal subarachnoid hemorrhage was conducted at three institutions in Mexico, Argentina, and Brazil between May 2002 and April 2003. Nineteen patients were treated with 20 procedures performed (one patient having received two procedures); sixteen patients had symptomatic vasospasm, two patients had asymptomatic vasospasm, and one patient who was in a barbiturate coma and was treated based on imaging evidence of vasospasm (compassionate use). Data regarding outcome is presented for the 16 patients with symptomatic vasospasm per the indication for this HDE. Adverse events (described in Section VII) were supplied for all 19 patients.

Patients who had failed maximal medical therapy for vasospasm were screened against the following criteria:
Inclusion criteria:

1) Age > 18.
2) Clinical evidence of vasospasm with angiographic confirmation OR
3) A perfusion deficit on Xenon CT, MRI perfusion scan or parenchymogram.
4) Informed Consent

Exclusion criteria:

1) Unsecured aneurysm(s)
2) Symptoms attributable to other causes (metabolic, infection, etc.)
3) Large infarct on CT scan
4) Hydrocephalus thought to be the cause of symptoms
5) Intracranial hemorrhage (not due to the aneurysm rupture)
6) Coagulopathy
7) Aortic diameter not between 12-23cm below the renal arteries and 12-27 above the renals
8) Aortic aneurysm
9) Renal insufficiency (creatinine 2x normal)
10) History of myocardial infarction, congestive heart failure or angina or ejection fraction < 40%
11) Femoral artery stenosis precluding device placement
12) Pregnancy

Patient Demographic:

Characteristics	Mexico	Argentina	Brazil	All Sites
Number	1 (s) 1 (a)	14 (s) 1 (a) 1 (c)	1 (s)	19
Age range (yrs)	56 & 61	31-63	30	30 - 63
Gender: Male/Female	1/1	5/11	1/0	7/12

S = symptomatic a = asymptomatic c = compassionate use

NeuroFlo treatment was administered by placing the device balloons under fluoroscopy on either side of the renal arteries. The infrarenal balloon was inflated first to 70% occlusion for 5 minutes, followed by inflation of the suprarenal balloon to 70% occlusion for an additional 40 minutes. At the end of the 45 minute inflation cycle, the balloons were slowly deflated.

Patients were administered an NIH Stroke Scale (NIHSS) test prior to NeuroFlo treatment, upon completion of treatment, at 24 hours and at 30 days. Clinical improvement was defined as a ≥ 3 point decrease in NIHSS.

Results

Information on clinical outcome (i.e., NIHSS) is provided in Table 1. Table 1 stratifies patients based on their Fisher score (a scale from 0-4 of the severity of the SAH, 4 being most severe) compared with their baseline, post-procedural, 24 hour and 30-day NIHSS scores. The Fisher score was taken upon presentation to the hospital at the time of SAH; the baseline NIHSS was taken once a patient was accepted for NeuroFlo treatment – an average of 9 days post-SAH.

Assuming that a decrease of ≥ 3 points in NIHSS from baseline to immediately post-treatment represents a significant neurologic improvement, 8/16 patients (50%) demonstrated such a clinically relevant response to NeuroFlo treatment that was sustained at 24 hours; of these 8, 7 had a presenting Fisher score of 4. Ten of 16 patients (63%) had a 3 point or greater decrease in NIHSSS at 30 days. In all but 2 cases, patients who received the NeuroFlo treatment had failed to respond to Triple-H and/or other medical therapies to treat their vasospasm.

There were 6 deaths total (32%); 4 occurred in the symptomatic group (25%). Adverse events leading to death included hydrocephalus with neurological deterioration (2), sepsis (1), neurological deterioration (1), stroke (1) and arrhythmia and organ failure (1). Other adverse events included anemia and neurological deterioration. Due to the small sample size, the reliability of these numbers is unknown.

Table 1
Outcome of Sixteen Patients with Symptomatic Vasospasm

Presenting Fisher	Baseline NIHSS	Immediate Post-Deflation NIHSS	24-Hour NIHSS	30-Day NIHSS
1	1	0	0	0
2	17	ND-Sedated	ND	ND-Died @ 84 hours
3	6	ND	9	0
3	10	2	2	1
3	2	2	1	See second Treatment
Second Treatment	3	1	3	0
4	15	12	13	5
4	8	1	1	0
4	21	19	18	ND-Died @ 8 Days
4	7	5	5	1
4	9	9	23	ND-Died @ 9 Days
4	6	2	0	0
4	11	7	5	ND-Died @ 4 Days
4	17	7	4	2
4	14	4	6	4
4	3	1	1	1
4	9	6	6	2

ND = not done

When the outcome data is stratified by baseline NIHSS (see Table 2), good outcome (at 30 days) was seen in 70% of patients with a good presenting score (10 or less) where as poor outcome was seen in 50% of patients with NIHSS > 10. The literature on SAH supports that the likelihood of a good outcome in the patients presenting with less severe disease is higher than for those presenting in worse neurologic condition. Therefore, the individual 30 day results shown could be related to the expected outcome in patients due to the natural history of the disease, and unrelated to treatment with the NeuroFlo device.

Table 2

BASELINE NIHSS	Total number of patients	Average group Baseline NIHSS	Good outcome	Poor outcome
0-10	10	6.5	7	3
>10	6	16	3	3

XI. RISK / PROBABLE BENEFIT ANALYSIS

Arterial cerebral vasospasm is characterized by a significant reduction in arterial luminal diameter caused by smooth muscle contraction of the vascular wall. The mechanisms responsible for SAH-induced vasospasm are poorly understood. Ultimately, the decrease in luminal diameter leads to a reduction in regional blood flow producing cerebral ischemia. Below a critical threshold value, cerebral ischemia leads to neurological symptoms such as lethargy, obtundation, or focal deficit. Untreated, critically hypoperfused tissue infarcts, causing stroke.

As stated in the intended use statement, use of the NeuroFlo catheter should be considered only after the patient has failed maximal medical management. These may include drug treatments, generally categorized to Triple-H therapy and intra-arterial vasodilators.

The NeuroFlo catheter is designed to partially obstruct the abdominal descending aorta thereby potentially increasing blood flow to the brain. Cerebral perfusion may be improved by diverting more blood through spastic vessels as well as by expansion of the collateral circulation. Improved regional perfusion may lead to symptomatic improvement

The risks associated with the NeuroFlo procedure include risks associated with placement of the catheter in the descending aorta, those attributable to the hemodynamic consequences of partial aortic obstruction in the descending aorta, and those associated with any femoral arterial catheterization

The NeuroFlo Catheter was studied in 19 vasospasm patients across 3 centers located outside the United States. 8/16 (50%) of the patients experienced an improvement in NIHSS scores $\geq$ 3 points 24 hours after the procedures. Six of the 8 patients had sustained improvement at 30 days (one patient died, one patient did not get tested). Additionally, 3 patients who showed <3 point improvement during the procedure exhibited a $\geq$3 point improvement in NIHSS at 30 days.

Angioplasty of the spastic vessels is another device option. The spastic vessels are dilated mechanically using a balloon catheter. The benefit of this procedure has not been proven. Given the limited treatment options available for patients with cerebral vasospasm who have failed maximal medical management, the probable benefits of treatment with the device (a potential improvement in symptoms related to cerebral ischemia) outweighs the risks.

XII. PANEL RECOMMENDATION

Panel review of this HDE application was not performed; it was determined that the preclinical and clinical issues raised by this HDE did not require panel review.

XIII. CDRH DECISION

CDRH had determined that, based on the data submitted in the HDE, that the NeuroFlo Catheter will not expose patients to an unreasonable or significant risk of illness or injury, and that the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order for the NeuroFlo Catheter HDE on 03/30/05.

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See the NeuroFlo Catheter 'Instructions for Use'

Hazards to Health from use of the Device: See Indications, Contraindications, Warnings, Precautions and Complications listed in the Instructions for Use.

Post-approval Requirements and Restrictions: See Approval Order